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8 September 1999

Dockets Management Branch (HFD-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Dear Sirs

Comments on FDA Draft Guidance For Industry; Docket # 98D-0077

Draft Guidance for Industry: Clinical Development Programs for Drugs, Devices and Biological Products Intended for the Treatment of Osteoarthritis (OA). Federal Register 64: 135; 15 July 1999

Procter & Gamble Pharmaceuticals (P&GP) agrees that clinical development of drugs offering more than symptomatic benefit in osteoarthritis (OA) is of great importance to the health of the nation. From the Arthritis Advisory Committee meeting of 21 July 1999, at which this revised draft guidance was discussed, P&GP understands that FDA may consider structure modifying osteoarthritis drugs as being appropriate for review under the accelerated approval rule (21 CFR 314 Subpart H), and welcomes this acknowledgement of the debilitating nature of OA. P&GP is therefore grateful for the opportunity to comment on this revised draft guidance which strives to guide industry in the development of structure modifying treatments for OA. P&GP is also pleased to observe reference to the relevant European regulatory Points to Consider in this revised draft FDA guidance document. P&GP has a number of comments, presented here in the order in which information appears in the guidance document;

Section II, Use of Preclinical Models: Paragraph 3, sentence 2. To avoid giving the impression that the two animal models of OA cited as examples constitute the only models accepted by the Agency, the statement should be rewritten as;
"Examples include, <u>but are not limited to</u> the guinea pig spontaneous OA model and the Pond Nuki dog model.

Section II, Use of Preclinical Models: Paragraph 4, bullet number 3. In evaluating possible usefulness of an animal model, this section calls for consideration of correlating joint structural changes with clinical changes, such as pain, in these animal models. P&GP considers that correlation of structural changes in animal models with pain/function is not feasible at this time. Animal pain study methods are irrelevant for OA structure/pain questions. Gait analysis is not useful in guinea pigs, and dogs limp after cruciate ligament surgery, but quickly recover co-incident with surgical healing. Furthermore, structural information in animal studies comes from post-mortem

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histologic examination, and serial radiographs have not proven to be useful in preclinical screening of chemical analogs. In order to avoid making this list of considerations too prescriptive, the last sentence of paragraph 3 should be rewritten as;
"When evaluating the possible usefulness of an animal model, consideration of the following questions ~~should~~ may be ~~considered~~ helpful."

Section IV, Osteoarthritis Measurements: Paragraph 1, P&GP notes the statement; "Protocols enrolling patients with knee or hip OA (the so-called signal joints) have made measuring and interpreting treatment effects easier, and the development of specific OA measurements has paralleled, and in some ways guided, this signal-joint approach. However, exclusive focus on the signal-joint will miss what is happening at other OA sites. Appropriate measurements, such as using a patient global assessment, or taking a specific non-signal-joint measurement, should be included to capture treatment effects at other OA sites". P&GP has also listened with interest to the questions regarding distribution of evidence from various OA sites that were discussed at the Arthritis Advisory Committee meeting, 21 July 1999.

P&GP shares the concerns of members of the Arthritis Advisory Committee regarding excessive splitting of the indication for a structure-modifying drug. P&GP believes that it is not appropriate to require studies in both hip and knee OA in order to secure an indication for treatment of OA in the weight-bearing joints. The CPMP Points to Consider (July 1998) states that studies showing structural benefit in knee OA will also receive a claim for hip OA, as the pathogenesis of the disease is the same in these weight-bearing joints. P&GP agrees with this requirement, and proposes that the FDA adopt this same position and document this in the OA guidance.

Section V.A. Treatment of Symptoms, Pain and Function: Paragraph 2 discusses trial duration, requiring studies of at least 3 months, except in the case of products where experience exists within the same class, in which case 6 weeks may be sufficient. P&GP considers that some drugs may provide benefit in acute treatment of minor pain associated with osteoarthritis, and for such products, a trial duration of 7-10 days would be sufficient.

Section V.B. Delay in Structural Progression: Paragraph 2, last sentence. The guidance conveys the implicit requirement here that regardless of expectations of effects on joint space narrowing (JSN) in a trial of a proposed structure-modifying drug, effects on symptoms must also be evaluated. P&GP agrees with this requirement, but wishes to clarify expectations for an acceptable outcome with respect to symptom modification in such a scenario. It was stated in the previous February 1998 draft OA guidance, and as discussed at the Arthritis Advisory Committee meeting 21 July 1999, that 'no worsening' of pain/function should be a requirement in a trial of a structure modifying drug. P&GP proposes that 'no worsening' should be defined as study drug and control being clinically similar based on a pre-defined delta. P&GP considers that it is more appropriate to base this decision on a statistical evaluation of a pre-defined clinical similarity, based on a larger delta than usually defined in 'statistical non-inferiority' trials. P&GP recognises that the majority of internal medicine diseases are treated with more than one medication. It is therefore logical to believe that a structure modifying osteoarthritis drug (which demonstrates no deleterious effect on pain and

symptoms in clinical studies) may be supplemented with 'as needed' analgesics in clinical practice.

Section V.B.3 Slow JSN by at least a pre-specified amount: P&GP acknowledges the correction to the draft guidance provided at the 21 July 1999 Arthritis Advisory Committee meeting that "sponsors seeking this claim should anticipate relatively large changes, greater than 50%, in slowing JSN relative to the control arm". P&GP shares the point of view of members of the Advisory Committee that as the clinically-relevant minimal difference in JSN has yet to be determined, differences of greater than 50% may not be required in order to provide clinical benefit in this patient population. P&GP supports the Committee's comments that differences within a range of 30-50% may be meaningful, however it is difficult to prospectively determine a clinically relevant difference in the absence of data. With the current paucity of data in this field, P&GP proposes that the FDA guidance requires simply that an appropriate pre-defined difference in JSN is observed, with no deleterious effects on pain and/or function.

Section VI. Trial Designs and Analyses: In addition to reviewing the revised draft guidance, P&GP has listened with interest to the discussions regarding data analysis at the 21July 1999 Arthritis Advisory Committee meeting. From a statistical analysis point of view, P&GP believes that there is no appreciable difference between research in OA or other diseases. P&GP therefore proposes that adjustments for multiple comparisons with regard to secondary endpoints (eg pain and function) and handling of missing data should be addressed in accordance with the ICH Guidance on Statistical Principles for Clinical Trials, and that this should not differ for this therapeutic area. The Guidance on Statistical Principles for Clinical Trials indicates that a universally accepted method of handling missing values does not currently exist and that the effect of the missing data for the primary analysis should be investigated. Also, the ICH guidance does not require adjustments for multiplicity due to secondary variables, but requires that the number of secondary variables be few and relevant to the scope of the trial. P&GP is also concerned that through comments concerning adjustments for multiplicity, the revised draft OA guidance implicitly suggests that studies in OA, with primary emphasis on structure-modification, should be powered for symptom-modifying secondary endpoints. If this were truly the intent, the sample size for phase III studies would be extremely large, posing an unduly burdensome requirement on study sponsors. P&GP therefore concludes that it is not appropriate for the revised draft OA guidance to contain specific guidance regarding adjustments for multiplicity or methods for handling missing data.

Yours faithfully

Wendy Sauber (for Susan Denegri)

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Section Head, US Regulatory Affairs

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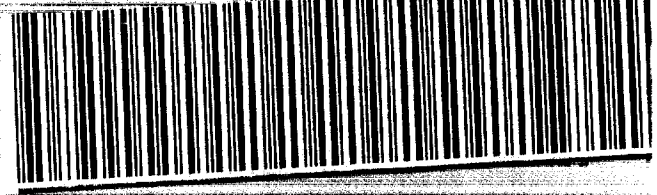

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